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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/475,784	06/07/95	LIVINGSTON	P 43016-C/JPW/

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EXAMINER	
HUNT, J	
ART UNIT	PAPER NUMBER
1642	31

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

[redacted]

Office Action Summary	Application No. 08/475,784	Applicant(s) Livingston
	Examiner Jennifer Hunt	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 23, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *78-93 and 95-100* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *78-93 and 95-100* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 7-30-2001 has been entered.

2. The Examiner and Art Unit for this case have changed. Please address future correspondence to Examiner Jennifer Hunt, Art Unit 1642.

3. Acknowledgment is made of applicant's cancellation of claim 94. Claims 78-93 and 95-100 are pending in the application and considered herein.

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Objections or Rejections Maintained

Specification

5. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

6. Claims 78-93, and 95-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-92 and 94-99 of copending Application No. 08/477,097 for reasons made of record in paper #23, mailed 10-5-1999, and paper #25, mailed 6-27-2000.

Applicant argues that the claims of 08/477,097 do not render obvious the instant claims. Applicant's arguments filed 7/30/2001 have been fully considered but they are not persuasive, because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

7. Claims 78-93, and 95-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 109-122 of copending Application Nos. 08/477,147 for reasons previously made of record in paper #23, mailed 10-5-1999, and paper #25, mailed 6-27-2000.

Applicant argues that the claims of 08/477,147 do not render obvious the instant claims. Applicant's arguments filed 7/30/2001 have been fully considered but they are not persuasive,

because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

8. Claims 78-93, and 95-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims 97-99, 101-111, and 113-118 of application No 08/196,154 for reasons previously made of record in paper #23, mailed 10-5-1999, and paper #25, mailed 6-27-2000.

Applicant argues that the claims of 08/196,154 do not render obvious the instant claims. Applicant's arguments filed 7/30/2001 have been fully considered but they are not persuasive, because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

9. Claims 78-81, 83-93, and 95-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office actions and reiterated below.

With regards to the addition grounds of rejection of claims 94-100 for the recitation of preventing cancer, these grounds are withdrawn in light of the amendments thereto.

With regard to the grounds of rejection of pending claims 78-81, 83-93, and 95-100 for the recitation of "Keyhole Limpet Hemocyanin or a derivative thereof", for reasons set forth in the previous office actions, derivatives are not enabled.

Applicant cites page 12, lines 4-13 for examples of generating KLH derivatives and argues that this provides enablement. Applicant's arguments filed 7/30/2001 have been fully considered but they are not persuasive.

As set forth in previous Office Actions, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). Rudinger et al. Teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a *priori* but must be determined from case to case by painstakingly experimental study" (see page 6). Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. Fox et al. Teach methods for determining fragments which have antigenic activity is unpredictable. These references demonstrate that a even a single

amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

Contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does **not** disclose the following :

- the general tolerance to modification and extent of such tolerance;

- specific positions which can be predictably modified; and

- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. Said disclosure is not commensurate in scope with the claimed invention. Said cite makes reference only to linking KLH to an "immunological adjuvant" **and not** amino acid modifications (i.e deletions, substitutions) of KLH. As set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). For the reason set forth above and in the previous Office Actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

10. The rejection of 78-93, 95, and 97-100 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-

4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is maintained for reasons made of record and reiterated herein.

Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). Livingston et al teach that the composition for treatment is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046, column 1, paragraph 3, and paragraph bridging p 7046-47). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). Livingston et al differ by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T

cell help necessary for the response (page 406, paragraph 1). Ritter et al teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

Ritter et al (1990) teach that GD3 lactone is more immunogenic than GD3.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method of Liane et al and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response that the commonly used adjuvant use by Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. It also would have been *prima facie* obvious to use doses of between 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within

the ordinary skill in the art and use the composition as modified supra for treatment of melanoma as taught by Livingston et al (Cancer Research) . It also would have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would react with the melanoma cells. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990) and would be expected to product an enhanced antibody response as compared to GD3. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ε-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

Applicant argues that the references do not teach, suggest or disclose applicant's invention. Specifically, applicant argues that the primary reference, Livingston et al. (1989) fails to teach conjugation of GM2 or other gangliosides by means of a carbon on the ceramide moiety

with aminolysyl groups on KLH in a composition or using this conjugate for treatment. Applicant further argues that the secondary references fail to supply this teaching.

With regard to Ritter et al. (1991), applicant acknowledges that Ritter et al. (1991) teaches conjugation of GM2 to KLH. Applicant argues that Ritter et al. (1991) fails to teach the chemical nature of the GM2-KLH conjugate, how to make the conjugate, and further does not disclose conjugation through the ceramide.

With regard to Ritter et al (1990), applicant argues that there is no teaching of conjugation to KLH, and further that modifications of the gangliosides of Ritter et al. (1990) are in the carbohydrate portion, not the ceramide portion. Applicant thus concludes that Ritter et al. (1990) teaches away from ceramide conjugation.

With regard to Liane et al., applicant supplies Helline et al. (Exhibit B), which applicant argues teaches that the Liane et al. method "is of limited use for the conjugation of gangliosides to carrier proteins because it requires acetylated, methyl ester derivatives of gangliosides to avoid coupling via the sialic acid carboxyl group. Deacylation after conjugation under basic conditions is necessary, conditions most proteins cannot be exposed to without degradation." Based on this teaching, applicant concludes that Liane et al. fails to supply the missing teachings of the primary reference. With regard to the other secondary references (Uemura et al., Kensil et al., Marcini et al. and Livingston et al (US Patent 5,102,663)) applicant argues that these references fail to teach a ceramide linkage. Applicant's arguments filed 7/23/2001 have been fully considered but they are not persuasive.

The conjugate and method of treatment taught in Livingston et al., as set forth above, teaches the instantly claimed conjugate, but fails to teach conjugation to KLH.

Ritter et al (1991) teaches that the conjugation of GM2 to KLH is desirable because it generates a superior immune response. With regard to Ritter et al. (1991), applicant's argument that the reference fails to teach the specific ceramide conjugation is not persuasive because such a conjugation was known in the art at the time the invention was made (as set forth in the additional secondary references). The key teaching of Ritter et al (1991) is that one would expect a superior immune response which GM2 is coupled to KLH. Thus Ritter et al. (1991) provides motivation to conjugate the ganglioside to KLH.

With regard to Ritter et al. (1990), applicant's arguments misrepresent the teachings of Ritter et al (1990) and the examiner's reasons for citing such. Ritter et al. (1990) was cited for the teaching that GD3 lactone is more immunogenic than GD3. The reference was not cited to represent ceramide linkage.

With regard to Liane et al., in contrast to applicant's arguments, Liane et al. does not require deacetylation after conjugation. It appears that the reaction that applicant had referred to is that of figure 2 in the Liane et al. paper, in which the deacetylation step occurs after glass beads have been conjugated to the ganglioside. Applicant is pointed to figure 1 of Laine et al., which contains a different reaction, which provides carbodiimide linkage under standard acidic, not basic conditions. The deacetylation step in the conjugation method of figure 1 occurs before the linkage step and the protein is not present in basic conditions when substituted for the

sepharose. It is further noted that the use of carbodiimide under conditions of Liane et al. have long been used for the coupling of peptides to carrier proteins and will not degrade the protein. With regard to the other secondary references (Uemura et al., Kensil et al., Marcini et al. and Livingston et al (US Patent 5,102,663)) applicant only argues that these references fail to teach a ceramide linkage, however they are not cited for the teaching of a ceramide linkage. Therefor the rejection is maintained for reasons of record.

11. Claim 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 78-93, and 95-100 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931).

The teachings of Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) are set forth supra. The combination differs by not teaching the administration of the composition for treating cancer of epithelial origin.

Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/ QS-21 composition or other ganglioside conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Applicant argues that Irie et al. does not supply the missing teaching of a ceramide linkage. Applicant's arguments filed 7/23/2001 have been fully considered but they are not persuasive.

As set forth above, the teaching of a ceramide linkage is not missing, and Irie et al. is not relied upon to teach such. Irie et al. teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31). Applicant has provided no arguments for such. Therefor the rejection is maintained for reasons of record.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Harlow and Lane, Antibodies A Laboratory Manual, Chapter 6, pages 84-85, 1988 is cited to demonstrate that carbodiimide linkages to carrier proteins were well known in the art at the time the invention was made (see pages 84-85).

Status of Claims

13. No claims are allowed.

Status of Claims

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

October 21, 2001

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